REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-37 were pending. In this response, claim 20 is cancelled and claims 1, 2, 9, 11, 13, 17, 21, 23, 28, and 30-32 have been amended for further clarity. Support for the amendments can be found in the specification and claims as originally filed. For example, the use of an agent that maintains the pH between about 5.5 and about 7.0 is disclosed, e.g., at page 9, line 31; and the use of an agent containing calcium or magnesium salts at a concentration of at least about 20 mM is disclosed, e.g., at page 4, line 18. No new matter is added. Accordingly, claims 1-19 and 21-37 are pending and at issue.

Double Patenting

Claims 1, 7, 8, 10-12, 14, 15, 17-19, and 24 have been rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-7, 11, 12, and 16-19 of copending application serial no. 10/602,340. This rejection is respectfully traversed.

Because the reference application has not issued as a patent, the Examiner is requested to allow the present claims to issue, after which terminal disclaimers can be filed (as applicable) in succeeding patent applications that mature to allowance.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 17, 27, and 28 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the terms "methionine-containing peptide" and "Factor VIIa sequence variant" encompass a great number of species.

In this response, claim 17 has been amended to delete the term "methionine-containing peptide", rendering moot this ground for rejection.

It is believed that this rejection is not appropriately applied to claims 27 and 28. The present claims are directed to formulations comprising as an active ingredient Factor VII or Factor VII-related polypeptides, i.e., molecules closely related to Factor VII. The claims are not directed to Factor VII or Factor VII variants per se, but rather to the elements that provide useful *formulations*. It is clear from the specification that Applicants, at the time of filing, contemplated not only

formulations comprising wild-type Factor VII but also formulations of Factor VII analogues and derivatives. In support, the specification at pages 13-15 describes Factor VII sequence variants, including specific examples of such variants as well as methods for ascertaining the biological activity of a particular variant polypeptide (as required by claim 28). Accordingly, it is believed that Applicants have more than fulfilled the written description requirement and that this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 9, 11, 13, 17, 21, 23, and 32 have been rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness, based on improper Markush language (claims 9, 11, 21, and 32); and the recitation of: "small" (claim 11); "concentration" (claim 13); "methionine analogue" and "methionine homologue" (claim 17); and "the buffer" (claim 23.)

In this response, claims 9, 11, 21, 23, and 32 have been amended to correct informalities, and claim 17 has been amended to delete the term "methionine homologue".

With respect to the term "methionine analogue", it is believed that this term is well-known in the art. The Examiner's attention is directed to the following articles (both of which are attached herewith): Cooper et al., "Biochemistry of Sulfur-Containing Amino Acids", *Ann.Rev.Biochem.* 52:187, 1983 (see, especially, pp 215-216); and Porter et al., "Growth Inhibition by Methionione Analog....", *Biochem.Biophys.Res.Comm.* 122:350, 1984 (see, especially, Figure 1.) Those of ordinary skill in the formulation arts understand the metes and bounds of methionine analogues; accordingly, it is respectfully submitted that this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 5-7, 10-12, 20-22, and 29-35 have been rejected under 35 U.S.C. § 102(b) as anticipated by Hannam et al., U.S. Patent No. 5,649,959. The Examiner contends that Hannam et al. discloses a fibrin sealant kit containing Factor VII in a Tris buffer at pH 7.5. This rejection is respectfully traversed.

In this response, claims 1, 21, 30, and 31 have been amended to require a pH between 5.5 and 7.0. Accordingly, Hannam et al. cannot anticipate the present claims, and this rejection should be withdrawn.

Claims 1-7, 9-16, 20-23, 25, 26, and 29-37 have been rejected under 35 U.S.C. § 102(b) as anticipated by The Medicine Catalogue (2000). The Examiner contends that the Medicine Cataloge discloses a Factor VIIa composition containing "105 mg calcium chloride[1], 1.3 mg glycylglycine, 30 mg mannitol, 3.0 mg sodium chloride and 0.1 mg polysorbate 80 per mL, wherein the composition has a pH of 5.4-6.0" (Office Action at page 7.)

In this response, claims 1, 21, 30, and 31 have been amended to require a concentration of a calcium or magnesium salt of at least 20 mM. By contrast, the formulation of The Medicine Catalogue contains either about 10 mM or 13 mM calcium chloride (based on a molecular mass of 111 g/mol for anhydrous and 147 g/mol dehydrate, respectively.) Accordingly, The Medicine Catalogue cannot anticipate the present claims, and this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 5, 6, 12, 13, 22, 23, 30, and 31-37 have been rejected under 35 U.S.C. § 103(a) as unpatentable over The Medicine Catalogue. The Examiner claims that it would be obvious to vary the concentrations of the components of the presently claimed formulation.

The present invention is directed towards liquid formulations of Factor VII and Factor VII analogues and derivatives that exhibit improved stability properties over previously available formulations. As discussed above, in this response the present claims have been amended to require a pH between about 5.5-7.0 and a concentration of calcium or magnesium of at least 20 mM.

Contrary to the Examiner's assertion, modulation of these parameters can have unexpected consequences on the suitability of particular protein formulations. For example, Figure 1 of the present specification demonstrates that raising the pH between 6.0 and 7.5 causes a dramatic increase in the amount of undesirable Factor VII aggregates after 3-months' storage at 2-8°C. This is not a result that could have been predicted. Furthermore, the present inventors have also found that Factor VII formulations are stabilized by providing certain concentrations of ions (including calcium); see, e.g., Example 9.

1 It is believed that the concentration of calcium chloride is a typographical error, as the English version of The Medicine Catalogue indicates a calcium chloride concentration of 1.5 mg/mL, and it is believed that this is what the Examiner intended.

By contrast, The Medicine Catalogue discloses a single formulation of Factor VII that was designed to be stored in a lyophilized form and reconstituted only immediately (i.e., within 24 h) before use. Nothing in The Medicine Catalogue disclosure would have led one of ordinary skill in the art to any reasonable expectation of achieving a liquid formulation exhibiting longer-term stability properties. On this basis, it is respectfully submitted that the presently claimed formulations are non-obvious over the cited reference.

Claim 8 has been rejected under 35 U.S.C. § 103(a) as unpatentable over The Medicine Catalogue in combination with WO 97/19687 (Miekka et al.); the Examiner contends that Miekka et al. discloses the equivalence of calcium, magnesium, and manganese ions for protein stabilization. Claims 17-19 have been rejected under 35 U.S.C. § 103(a) as unpatentable over The Medicine Catalogue in combination with Thatcher et al., US 5,830,852; the Examiner contends that Thatcher discloses the use of methionine as an antioxidant in peptide-containing compositions. Claim 24 has been rejected under 35 U.S.C. § 103(a) as unpatentable over The Medicine Catalogue in combination with Osawa et al., US 5,993,795; the Examiner contends that Osawa et al. discloses the use of methyl and propyl paraben as preservatives in protein-containing solutions. In all of these rejections, the Examiner further contends that it would have been obvious to combine each of the cited disclosures with The Medicine Catalogue Factor VII formulation to achieve the presently claimed invention. These rejections are respectfully traversed.

As discussed above, it is believed that the present invention, as broadly claimed, is non-obvious over The Medicine Catalogue. None of the secondary references remedies the deficiencies of The Medicine Catalogue with respect to any of the supplemental individual components of the presently claimed formulations. For example, it is not disputed that methionine and methyl or propyl paraben were known as components of protein formulations; however, neither Osawa et al. nor Thatcher et al. contains any disclosure that would, either alone or in combination with The Medicine Catalogue, render obvious the formulations of the present invention. Accordingly, it is respectfully submitted that the presently claimed invention is non-obvious over all of the cited references and that these rejections should be withdrawn.

In view of the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

Date: August 7, 2006

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